

CM We claim:

1. A compound of the formula PS

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (L) A

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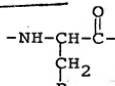
(I)

PS and the pharmaceutically acceptable salts thereof wherein:

φ V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

φ W is tyrosyl, phenylalanyl or 3-(1-pentafluoro-phenyl)-L-alanyl;

φ X is a D-amino acid,



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(<sup>β,γ</sup>-) where R is

φ (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

φ (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenylyl, perhydro-2,2-diphenylmethyl and adamantlyl;

φ Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

φ Z is glycinate or  $\text{NH}_2\text{R}^1$ , wherein

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25

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R<sup>1</sup> is lower alkyl, cycloalkyl, fluoro lower alkyl or  
-NH-C(=O)-NH-R<sup>2</sup> wherein  
~~Tyrosyl~~  
R<sup>1</sup>, R<sup>2</sup> is hydrogen or lower alkyl.

5        2. The compound of claim 1 wherein V is  
tryptophyl or phenylalanyl; W is tyrosyl; X is  
3-(2-naphthyl)-D-alanyl or 3-(2,4,6-trimethylphenyl)-D=  
alanyl; Y is leucyl or N-methyl-leucyl; and Z is glycine=  
<sup>NHET</sup> amide or ~~prolylethylamide~~.

10      3. The compound of claim 2 wherein X is  
3-(2-naphthyl)-D-alanyl.

15      4. The compound of Claim 2 which is (pyro)Glu=D  
His-Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro=  
Gly-NH<sub>2</sub> and the pharmaceutically acceptable acid salts  
thereof.

20      5. The compound of Claim 3 which is (pyro)Glu=D  
His-Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-N-methyl-Leu-Arg=  
Pro-Gly-NH<sub>2</sub> and the pharmaceutically acceptable salts  
thereof.

25      6. The compound of claim 3 which is (pyro)Glu-His=D  
Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-NHET and  
the pharmaceutically acceptable salts thereof.

30      7. The compound of Claim 3 which is (pyro)Glu-His=D  
Trp-Ser-Tyr-3-(2-naphthyl)-D-alanyl-N-methyl-Leu-Arg-Pro=  
NHET and the pharmaceutically acceptable salts thereof.

8. The compound of Claim 3 which is (pyro)Glu-His-Phe-Ser-Syr-3-(2-naphthyl)-D-alanyl-Leu-Arg-Pro-Gly-NH<sub>2</sub> and the pharmaceutically acceptable salts thereof.

5 9. The compound of Claim 2 wherein X is 3-(2,4,6-trimethylphenyl)-D-alanyl.

10 10. The compound of Claim 9 which is (pyro)Glu-His-Trp-Ser-Tyr-3-(2,4,6-trimethylphenyl)-D-alanyl-Leu-Arg-Pro-Gly-NH<sub>2</sub> and the pharmaceutically acceptable salts thereof.

15 11. A method of inhibiting ovulation in a female mammalian subject which method comprises administering to said subject an effective amount of a compound of the formula P<sub>S</sub>

20  $\text{P}_S = (\text{pyro})\text{Glu}-\text{His}-\text{V}-\text{Ser}-\text{W}-\text{X}-\text{Y}-\text{Arg}-\text{Pro}-\text{Z} \text{ TM } (I) \text{ P}_S$

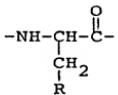
(I)

P<sub>S</sub> or a pharmaceutically acceptable salt thereof wherein:

P<sub>V</sub> is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

25 P<sub>W</sub> is tyrosyl, phenylalanyl or 3-(1-pentafluoro-phenyl)-L-alanyl;

a P<sub>X</sub> is a D-amino acid residue



70520X

(P.F.D.) wherein R is

5         $\text{P}_1$  (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

10       $\text{P}_1$  (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl perhydروبiphenylyl, perhydro-2,2-diphenylmethyl and adamantyl;

15       $\text{P}_1$  Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

$\text{P}_1$  Z is glycaminamide or  $\text{N}^{\text{H}}\text{NH}^{\text{H}}\text{R}^1$ , wherein

$\text{P}_1$   $\text{R}^1$  is lower alkyl, cycloalkyl, fluoro lower alkyl or

705211  $\text{-NH}-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{NH}-\text{R}^2$  wherein

20       $\text{P}_1$   $\text{R}^2$  is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

a ~~adjust~~ 12. A pharmaceutical composition ~~for inhibition of ovulation in a female mammal comprising a compound of the formula PS~~

25 ~~B1~~ formula PS

71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) P

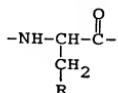
(I)

PS or a pharmaceutically acceptable salt thereof wherein:

P<sub>1</sub> V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

5 P<sub>1</sub> W is tyrosyl, phenylalanyl or 3-(1-pentafluoro-phenyl)-L-alanyl;

a P<sub>1</sub> X is a D-amino acid residue



TO 530 X

10 P<sub>1</sub> ) wherein R is

P<sub>2</sub> (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

15 P<sub>2</sub> (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydروبiphenylyl, perhydro-2,2-diphenylmethyl and adamantyl;

P<sub>1</sub> Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

P<sub>1</sub> Z is glycinate or  $\text{NH}_2\text{R}^1$ , wherein

20 P<sub>1</sub> R<sup>1</sup> is lower alkyl, cycloalkyl, fluoro lower alkyl or

TO 531X P<sub>1</sub>  $\text{NH}-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{NH}-\text{R}^1$  wherein

25 P<sub>1</sub> R<sup>2</sup> is hydrogen or lower alkyl, in admixture with a pharmaceutically acceptable non-toxic carrier.

13. A method of treating endometriosis in a female

30 mammalian subject which method comprises administering to

said subject an effective amount of a compound of the formula  $\text{P}_5$

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71 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I)  $\text{P}_6$

(I)

$\text{P}_5$  or a pharmaceutically acceptable salt thereof wherein:

10

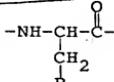
$\text{P}_6$  V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

$\text{P}_6$  W is tyrosyl, phenylalanyl or 3-(1-pentafluoro-phenyl)-L-alanyl;

a

$\text{P}_6$  X is a D-amino acid residue

15



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(P<sub>1+10</sub>) wherein R is

20

$\text{P}_2$  (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenlyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

25

$\text{P}_2$  (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenylyl, perhydro-2,2-diphenylmethyl and adamantyl;

30

$\text{P}_6$  Y is leucyl, isoleucyl, nor-leucyl or N-methyl-

leucyl;

f z is glycynamide or  $\text{NH}-\text{R}^1$ , wherein

A  $\text{R}^1$  is lower alkyl, cycloalkyl, fluoro lower alkyl or

TESON  $\text{O}-\text{C}-\text{NH}-\text{R}^2$  wherein

5  $\text{R}^2$  is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

10 14. A pharmaceutical composition for treatment of endometriosis in a female mammal comprising a compound of the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

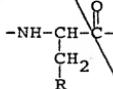
(I),

15 or a pharmaceutically acceptable salt thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

20 W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



25 wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl

5 groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycinate or -NH-R<sup>1</sup>, wherein

R<sup>1</sup> is lower alkyl, cycloalkyl, fluoro lower alkyl or -NH-C(=O)-NH-R<sup>2</sup> wherein

R<sup>2</sup> is hydrogen or lower alkyl, in addition with a pharmaceutically acceptable, non-toxic carrier.

15 14. A method of treating benign prostatic hypertrophy in a male mammalian subject which method comprises administering to said subject an effective amount of a compound of the formula  $\text{RS}$

20 Tl (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TM (I) RS

(I)  $\text{RS}$

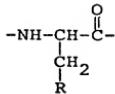
25  $\text{RS}$  or a pharmaceutically acceptable salt thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid  $\text{reada}$

30.



70570X

wherein R is

- 5      f<sub>1</sub> (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or
- 10     f<sub>1</sub> (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenylyl, perhydro-2,2-diphenylmethyl and adamantlyl;
- 15     f<sub>2</sub> Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;
- 16     f<sub>3</sub> Z is glycynamide or  $\text{NH}_2\text{R}^1$ , wherein
- 17     f<sub>4</sub> R<sup>1</sup> is lower alkyl, cycloalkyl, fluoro lower alkyl or  $\text{NH}-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{NH-R}^2$  wherein
- 20     f<sub>5</sub> R<sup>2</sup> is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

- 25     16. A pharmaceutical composition for treatment of benign prostatic hypertrophy in a male mammal comprising a compound of the formula

~~(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z~~

(I)

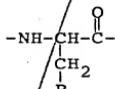
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or a pharmaceutically acceptable salt thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



wherein R is

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenylyl, perhydro-2,2-diphenylmethyl and adamantlyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycinate or  $-\text{NH}-\text{R}^1$ , wherein

$\text{R}^1$  is lower alkyl, cycloalkyl, fluoro lower alkyl or  $-\text{NH}-\overset{\text{O}}{\underset{\text{R}^2}{\text{C}}}-\text{NH}-\text{R}^1$  wherein

$\text{R}^2$  is hydrogen or lower alkyl, in admixture with a pharmaceutically acceptable, non-toxic carrier.

A method of inhibiting spermatogenesis in a male mammalian subject which method comprises

administering to said subject an effective amount of a compound of the formula PS

T1 (pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z TMT (E) R<sup>2</sup>

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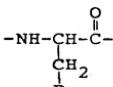
(I)

PS or a pharmaceutically acceptable salt thereof wherein:

P<sub>1</sub> V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

P<sub>1</sub> W is tyrosyl, phenylalanyl or 3-(1-pentafluoro-phenyl)-L-alanyl;

P<sub>1</sub> X is a D-amino acid residue



P<sub>2</sub> (a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenlyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

P<sub>2</sub> (b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenylyl, perhydro-2,2-diphenylmethyl and adamantyl;

P<sub>3</sub> Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

P<sub>4</sub> Z is glycinate or  $\frac{1}{n} \text{NH}-\text{R}^1$ , wherein

R<sup>1</sup> is lower alkyl, cycloalkyl, fluoro lower alkyl or  
TG00Y -NH-C(=O)-NH-R<sup>2</sup> [wherein]

R<sup>2</sup> is hydrogen or lower alkyl, or a pharmaceutical composition containing same.

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18. A pharmaceutical composition for inhibiting spermatogenesis in a male mammal comprising a compound of the formula

10

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z  
(I)

and the pharmaceutically acceptable salts thereof wherein:

15

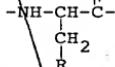
V is tryptophyl, phenylalananyl or 3-(1-naphthyl)-L-alanyl;

15

W is tyrosyl, phenylalananyl or 3-(1-pentafluorophenyl)-L-alanyl;

20

X is a D-amino acid



wherein R is

25

(a) a carbocyclic aryl-containing radical selected from the group consisting of naphthyl, anthryl, fluorenyl, phenanthryl, biphenylyl, benzhydryl and phenyl substituted with three or more straight chain lower alkyl groups; or

30

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-

naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl  
and adamantyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

Z is glycinate or  $-\text{NH}-\text{R}^1$ , wherein

R<sup>1</sup> is lower alkyl, cycloalkyl, fluoro lower alkyl or  
 $-\text{NH}-\overset{\text{O}}{\underset{\text{C}}{\text{C}}}-\text{NH}-\text{R}^2$  wherein

R<sup>2</sup> is hydrogen or lower alkyl, in admixture with a  
pharmaceutically acceptable, non-toxic carrier.

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19. A process for the preparation of a compound of  
the formula

(pyro)Glu-His-V-Ser-W-X-Y-Arg-Pro-Z

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(I)

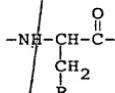


and the pharmaceutically acceptable salts thereof wherein:

V is tryptophyl, phenylalanyl or 3-(1-naphthyl)-L-alanyl;

W is tyrosyl, phenylalanyl or 3-(1-pentafluorophenyl)-L-alanyl;

X is a D-amino acid



25

wherein R is

(a) a carbocyclic aryl-containing radical selected  
from the group consisting of naphthyl, anthryl,  
fluorenyl, phenanthryl, biphenylyl, benzhydryl and phenyl

30

substituted with three or more straight chain lower alkyl groups; or

(b) a saturated carbocyclic radical selected from the group consisting of cyclohexyl substituted with three or more straight chain lower alkyl groups, perhydro-naphthyl, perhydrobiphenyl, perhydro-2,2-diphenylmethyl and adamanyl;

Y is leucyl, isoleucyl, nor-leucyl or N-methyl-leucyl;

z is glycaminamide or -NH-R<sup>1</sup>, wherein

R<sup>1</sup> is lower alkyl, cycloalkyl, fluoro lower alkyl or  
-NH-C(=O)-NH-R<sup>2</sup> wherein

R<sup>2</sup> is hydrogen or lower alkyl, which process comprises:

(i) removing protecting groups and optionally covalently bound solid support from a protected polypeptide to afford a compound of Formula (I) or a salt thereof, and optionally

(ii) converting a compound of Formula (I) to a pharmaceutically acceptable salt,

(iii) converting a salt of a compound of Formula (I) to a pharmaceutically acceptable salt, or

(iv) decomposing a salt of a compound of Formula (I) to a free polypeptide of Formula (I).